

10 **BLISTER PACKAGES AND ASSOCIATED METHODS OF FABRICATING
DRY POWDER DRUG CONTAINMENT SYSTEMS**

Related Applications

This application claims priority to U.S. Provisional Application Serial No. 60/514,733 filed October 27, 2003 and U.S. Provisional Application Serial No. 15 60/605,484 filed August 30, 2004, the contents of the above applications are hereby incorporated by reference as if recited in full herein.

Field of the Invention

20 The present invention relates to drug containment systems suitable for dry powders formulated for delivery as inhalant aerosols.

Background of the Invention

Dry powder inhalers (DPI's) represent a promising alternative to pressurized pMDI (pressurized metered dose inhaler) devices for delivering drug aerosols without 25 using CFC propellants. *See generally*, Crowder et al., 2001: *an Odyssey in Inhaler Formulation and Design*, Pharmaceutical Technology, pp. 99-113, July 2001; and Peart et al., *New Developments in Dry Powder Inhaler Technology*, American Pharmaceutical Review, Vol. 4, n.3, pp. 37-45 (2001). Typically, the DPIs are configured to deliver a powdered drug or drug mixture that includes an excipient 30 and/or other ingredients. Conventionally, many DPIs have operated passively, relying on the inspiratory effort of the patient to dispense the drug provided by the powder. Unfortunately, this passive operation can lead to poor dosing uniformity because inspiratory capabilities can vary from patient to patient (and sometimes even use-to-use by the same patient, particularly if the patient is undergoing an asthmatic attack or 35 respiratory-type ailment which tends to close the airway).

Generally described, known single and multiple dose dry powder DPI devices use: (a) individual pre-measured doses, such as capsules containing the drug, which can be inserted into the device prior to dispensing; or (b) bulk powder reservoirs which are configured to administer successive quantities of the drug to the patient via a dispensing chamber which dispenses the proper dose. *See generally* Prime et al., *Review of Dry Powder Inhalers*, 26 Adv. Drug Delivery Rev., pp. 51-58 (1997); and Hickey et al., *A new millennium for inhaler technology*, 21 Pharm. Tech., n. 6, pp. 116-125 (1997).

In operation, DPI devices strive to administer a uniform aerosol dispersion amount in a desired physical form (such as a particulate size) of the dry powder into a patient's airway and direct it to a desired deposit site(s). If the patient is unable to provide sufficient respiratory effort, the extent of drug penetration, especially to the lower portion of the airway, may be impeded. This may result in premature deposit of the powder in the patient's mouth or throat.

A number of obstacles can undesirably impact the performance of the DPI. For example, the small size of the inhalable particles in the dry powder drug mixture can subject them to forces of agglomeration and/or cohesion (*i.e.*, certain types of dry powders are susceptible to agglomeration, which is typically caused by particles of the drug adhering together), which can result in poor flow and non-uniform dispersion. In addition, as noted above, many dry powder formulations employ larger excipient particles to promote flow properties of the drug. However, separation of the drug from the excipient, as well as the presence of agglomeration, can require additional inspiratory effort, which, again, can impact the stable dispersion of the powder within the air stream of the patient. Unstable dispersions may inhibit the drug from reaching its preferred deposit/destination site and can prematurely deposit undue amounts of the drug elsewhere.

Further, many dry powder inhalers can retain a significant amount of the drug within the device, which can be especially problematic over time. In addition, the hygroscopic nature of many of these dry powder drugs may also require that the device be cleansed (and dried) at periodic intervals.

Some inhalation devices have attempted to resolve problems attendant with conventional passive inhalers. For example, U.S. Patent No. 5,655,523 proposes a

dry powder inhalation device which has a deagglomeration/aerosolization plunger rod or biased hammer and solenoid, and U.S. Patent No. 3,948,264 proposes the use of a battery-powered solenoid buzzer to vibrate the capsule to effectuate the release of the powder contained therein. These devices propose to facilitate the release of the dry powder by the use of energy input independent of patient respiratory effort. U.S. Patent No. 6,029,663 to Eisele et al. proposes a dry powder inhaler delivery system with a rotatable carrier disk having a blister shell sealed by a shear layer that uses an actuator that tears away the shear layer to release the powder drug contents. The device also proposes a hanging mouthpiece cover that is attached to a bottom portion of the inhaler. U.S. Patent No. 5,533,502 to Piper proposes a powder inhaler using patient inspiratory efforts for generating a respirable aerosol and also includes a rotatable cartridge holding the depressed wells or blisters defining the medicament holding receptacles. A spring-loaded carriage compresses the blister against conduits with sharp edges that puncture the blister to release the medication that is then entrained in air drawn in from the air inlet conduit so that aerosolized medication is emitted from the aerosol outlet conduit. The contents of these patents are hereby incorporated by reference as if stated in full herein.

More recently, Hickey et al., in U.S. Patent Application Serial No. 10/434,009 and PCT Patent Publication No. WO 01/68169A1 and related U.S. National Stage Patent Application Serial No. 10/204,609, have proposed a DPI system to actively facilitate the dispersion and release of dry powder drug formulations during inhalation using piezoelectric polymer film elements which may promote or increase the quantity of fine particle fraction particles dispersed or emitted from the device over conventional DPI systems. The contents of these documents are hereby incorporated by reference as if recited in full herein.

Notwithstanding the above, there remains a need for alternative blister packages that can be used with dry powder inhalers.

Summary of Embodiments of the Invention

Embodiments of the present invention provide blister packages that can be used with dry powder inhalers. The blister packages may be configured to employ active piezoelectric polymer-driven dispersion. Other embodiments are related to methods of fabricating blister packages that can be used in inhalers.

Certain embodiments are directed to multi-dose blister packages having a plurality of blisters thereon and adapted for use in an inhaler.

Some embodiments are directed to multi-dose blister packages having a plurality of blisters thereon and adapted for use in an inhaler. The packages include:

5 (a) a frame member having opposing top and bottom surfaces with a plurality of spaced apart gap spaces, a respective gap space configured to define at least a portion of a sidewall of a respective blister; and (b) a floor comprising a flexible material attached to the bottom surface of the intermediate member so that the floor extends under each gap space to define a bottom of each blister.

10 In some embodiments the blister packages can include: (a) an intermediate member having opposing top and bottom surfaces with a plurality of spaced apart gap spaces formed therethrough, a respective one gap space configured to define at least portion of a sidewall of a respective blister; (b) a ceiling attached to the top surface of the intermediate member so that the ceiling extends above each gap space to define a 15 top of each blister; and (c) a floor comprising a flexible material attached to the bottom surface of the intermediate layer so that the floor extends under each gap space to define a bottom of each blister.

In particular embodiments, the ceiling comprises a flexible material having sufficient structural rigidity so that the ceiling is able to define a plurality of spaced 20 apart projections therein and the intermediate member is substantially rigid. In some embodiments, the floor comprises a piezoelectric polymer and the blister package further includes a bolus quantity of dry powder disposed in respective blisters.

Other embodiments are directed to multi-dose blister packages adapted for use in an inhaler. The blister packages include: (a) a frame member having a plurality of 25 spaced apart apertures; (b) a ceiling disposed over the frame apertures; and (c) a flexible floor underlying and attached to the ceiling, wherein the ceiling and floor are configured to define a plurality of spaced apart sealed blisters therebetween.

The frame member can be configured to resist flexure. In some embodiments, the frame member can have a substantially planar body with sufficient rigidity to 30 remain substantially planar during operation.

The ceiling can be flat or be configured to have a plurality of spaced apart projections. In particular embodiments, the frame member can be configured with a

closed primary surface that defines the ceiling. In other embodiments, a respective ceiling projection extends through and rises above a respective frame aperture. The ceiling and/or the floor can comprise a piezoelectric polymer material. In certain embodiments, the ceiling is a substantially continuous layer that is sized and 5 configured to extend over all of the blisters under the frame member with the projections aligned to reside in the frame member apertures.

Other embodiments are directed to methods for fabricating a multi-dose blister package having a plurality of blisters thereon that is adapted for use in an inhaler. The method includes: (a) providing a substantially rigid member having opposing top 10 and bottom surfaces with a plurality of spaced apart gap spaces formed therethrough, a respective gap space configured to define at least a portion of a sidewall of a respective blister; (b) attaching a ceiling to the top surface of the intermediate member so that, in operation, the ceiling extends above each gap space to define a top of each blister; (c) disposing or positioning a quantity of dry powder in the blisters; and (d) 15 sealing a floor comprising a flexible material to the bottom surface of the intermediate member so that the floor extends under each gap space to define a bottom of each blister.

Still other methods making a multi-dose blister package adapted for use in an inhaler include: (a) providing a generally rigid frame member having opposing top 20 and bottom surfaces with a plurality of spaced apart gap spaces, a respective gap space configured to define at least a portion of a sidewall of a respective blister; (b) placing a metered quantity of dry powder in each of the blisters; and (c) sealing a floor comprising a flexible material to the bottom surface of the intermediate member so that the floor extends under each gap space to define a bottom of each blister.

25 In particular embodiments, the methods can include: (a) providing a frame member having a plurality of spaced apart apertures; (b) forming a plurality of spaced apart wells in a ceiling that, in position on a sealed blister package, define projections; (c) positioning a ceiling having the spaced apart wells above the frame and aligned therewith so that a respective ceiling well extends through and falls below a 30 respective frame aperture; (d) placing a quantity of dry powder in the ceiling wells; and (e) sealing a flexible floor to the ceiling to define a plurality of spaced apart sealed blisters therebetween.

In some embodiments, the frame member can be configured to resist flexure and the floor can comprise a piezoelectric polymer material.

In yet other embodiments, the present invention is directed to multi-dose dry powder packages that include: (a) a polymeric frame body comprising a plurality of spaced apart drug apertures; (b) a meted quantity of dry powder medicament held in each of the drug apertures; and (c) a detachable floor attached to the frame body apertures.

The polymeric frame body may have an upper primary surface that defines a generally rigid ceiling over the plurality of spaced apart drug apertures. In other 10 embodiments, the spaced apart apertures are through apertures, the package further comprising a sealant layer disposed over the frame body to define a ceiling over each of the apertures.

It is noted that aspects of the invention may be embodied as hardware, software or combinations of same, *i.e.*, devices and/or computer program products. 15 These and other objects and/or aspects of the present invention are explained in detail in the specification set forth below.

Brief Description of the Drawings

Figure 1A is an exploded view of an exemplary blister package according to 20 embodiments of the present invention.

Figure 1B is an exploded view of another exemplary blister package according to embodiments of the present invention.

Figure 1C is an exploded view of an additional exemplary blister package according to embodiments of the present invention.

Figure 1D is an exploded view of yet another exemplary blister package according to embodiments of the present invention.

Figure 2 is an enlarged perspective view of an assembled blister package according to embodiments of the present invention.

Figure 3 is a greatly enlarged section view of a portion of the blister package 30 taken along line 3-3 as shown in **Figure 2**.

Figure 4A is an enlarged side sectional view of a portion of a blister package taken along line 4-4 of **Figure 2**, illustrating a blister according to embodiments of the present invention.

5 **Figure 4B** is an enlarged side sectional view of a portion of a blister package taken along line 4-4 of **Figure 2**, illustrating a blister according to other embodiments of the present invention.

Figure 5A is an exploded view of another blister package according to embodiments of the present invention.

10 **Figure 5B** is a perspective view of the blister package shown in **Figure 5A** assembled.

Figure 5C is an enlarged side sectional view of a portion of the blister package shown line 5C-5C in **Figure 5B** illustrating a blister according to embodiments of the present invention.

15 **Figure 6** is a perspective view of a blister package assembly according to embodiments of the present invention.

Figures 7A-7C are perspective views of alternative blister packages suitable for concurrent dispensing of a plurality of separately held medicaments or dry powders according to embodiments of the present invention.

20 **Figure 8A** is a top or bottom view of an exemplary piezoelectric film layer according to embodiments of the present invention.

Figures 8B and 8C are top or bottom views of examples of a primary surface opposing of the surface shown in **Figure 8A** according to embodiments of the present invention.

25 **Figure 8D** is a top or bottom view of an alternative conductive pattern layer according to embodiments of the present invention.

Figures 8E is a top or bottom view of yet another conductive pattern layer according to embodiments of the present invention.

Figure 9 is a top perspective view of a blister package according to additional embodiments of the present invention.

30 **Figure 10** is a top perspective view of yet another blister package similar to that shown in **Figure 9**, but without the gear component, according to embodiments of the present invention.

Figure 11 is an exploded view of components that may be used to form the blister package shown in **Figure 9** or **10** according to embodiments of the present invention.

5 **Figures 12A and 12B** are enlarged partial side section views of a blister package such as those shown along line 12-12 in **Figure 10** illustrating exemplary blister configurations according to embodiments of the present invention.

Figure 13 is a block diagram of a control system with computer program code that may be included on a blister package and/or communicate with an inhaler according to embodiments of the present invention.

10 **Figure 14** is a block diagram of a control system and/or data processing system according to embodiments of the present invention.

Figure 15 is a flow chart of operations that can be carried out to fabricate a blister package according to embodiments of the present invention.

15 **Figure 16** is a flow chart of operations that can be carried out to fabricate a blister package according to other embodiments of the present invention.

Figure 17A is a flow chart of operations that can be carried out to fabricate a blister package according to further embodiments of the present invention.

Figures 17B-17D illustrate a serial progression of configurations of a blister package during the fabrication operations shown in **Figure 17A**.

20 **Figure 18** is a flow chart of operations that can be used to form a floor of a blister package according to embodiments of the present invention.

Figure 19A is a flow chart of operations that can be carried out to fabricate a laminated floor of a blister package according to embodiments of the present invention.

25 **Figures 19B-19E** illustrate a serial progression of configurations of piezoelectric floors suitable for a blister package during the fabrication operations shown in **Figure 19A**.

Description of Embodiments of the Invention

30 The present invention will now be described more fully hereinafter with reference to the accompanying figures, in which embodiments of the invention are shown. This invention may, however, be embodied in many different forms and

should not be construed as limited to the embodiments set forth herein. Like numbers refer to like elements throughout. In the figures, certain layers, components or features may be exaggerated for clarity, and broken lines illustrate optional features or operations unless specified otherwise. In addition, the sequence of operations (or 5 steps) is not limited to the order presented in the figures and/or claims unless specifically indicated otherwise. Where used, the terms "attached", "connected", "contacting", and the like, can mean either directly or indirectly, unless stated otherwise.

In the description of the present invention that follows, certain terms are 10 employed to refer to the positional relationship of certain structures relative to other structures. As used herein, the term "front" or "forward" and derivatives thereof refer to the general or primary direction that the dry powder travels as it is dispensed to a patient from a dry powder inhaler; this term is intended to be synonymous with the term "downstream," which is often used in manufacturing or material flow 15 environments to indicate that certain material traveling or being acted upon is farther along in that process than other material. Conversely, the terms "rearward" and "upstream" and derivatives thereof refer to the direction opposite, respectively, the forward or downstream direction.

It will be understood that the spatially relative terms are intended to 20 encompass different orientations of the device in use or operation in addition to the orientation depicted in the figures. For example, if a blister package shown in the figures oriented upward is inverted (turned over), elements described as "below" or "beneath" other elements or features would then be oriented "above" the other elements or features. Thus, the exemplary term "below" can encompass both an 25 orientation of above and below. The device may be otherwise oriented (rotated 90 degrees, 180 degrees, or at other orientations) and the spatially relative descriptors (such as, but not limited to, vertical, horizontal, above, upper, lower, below and the like) used herein interpreted accordingly.

Unless otherwise defined, all terms (including technical and scientific terms) 30 used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. It will be further understood that terms, such as those defined in commonly used dictionaries, should be interpreted as having

a meaning that is consistent with their meaning in the context of the relevant art and should not be interpreted in an idealized or overly formal sense unless expressly so defined herein.

The term "blister" means a sealed dry powder well, compartment or receptacle that can releasably hold a (typically meted bolus) quantity of a dry powder, typically a dry powder medicament. As such, the term "blister" is not limited to a particular shape or configuration (*i.e.*, is not limited to a raised surface configuration). The term "blister package" describes a device (such as a card) that holds a plurality of sealed blisters and may be also known as a drug containment system ("DCS"). In particular 5 embodiments, the blisters may be configured with planar ceilings and or floors, in other embodiments the ceiling and/or floor may have a projecting configuration, or configured in other suitable geometries, as will be described further below. The term "sealant layer" and/or "sealant material" includes configurations that have at least one 10 layer or one material; thus, such a phrase also includes multi-layer or multi-material 15 sealant configurations.

The devices and methods of the present invention may be particularly suitable for holding doses of dry powder substances that are formulated for *in vivo* inhalant dispersion (using an inhaler) to subjects, including, but not limited to, animal and, typically, human subjects. The dry powder substance may include one or more active 20 pharmaceutical constituents as well as biocompatible additives that form the desired formulation or blend. As used herein, the term "dry powder" is used interchangeably with "dry powder formulation" and means the dry powder can comprise one or a plurality of constituents or ingredients with one or a plurality of (average) particulate size ranges. The term "low-density" dry powder means dry powders having a density 25 of about 0.8 g/cm³ or less. In particular embodiments, the low-density powder may have a density of about 0.5 g/cm³ or less. The dry powder may be a dry powder with cohesive or agglomeration tendencies.

In any event, individual dispensable quantities of dry powder formulations can be a single ingredient or a plurality of ingredients, whether active or inactive. The 30 inactive ingredients can include additives added to enhance flowability or to facilitate aerosolization delivery to the desired systemic target. The dry powder drug formulations can include active particulate sizes that vary. The device may be

particularly suitable for dry powder formulations having particulates which are in the range of between about 0.5-50 μ m, typically in the range of between about 0.5 μ m - 20.0 μ m, and more typically in the range of between about 0.5 μ m -8.0 μ m. The dry powder formulation can also include flow-enhancing ingredients, which typically 5 have particulate sizes that may be larger than the active ingredient particulate sizes. In certain embodiments, the flow-enhancing ingredients can include excipients having particulate sizes on the order of about 50-100 μ m. Examples of excipients include lactose and trehalose. Other types of excipients can also be employed, such as, but not limited to, sugars which are approved by the United States Food and Drug 10 Administration (“FDA”) as cryoprotectants (e.g., mannitol) or as solubility enhancers (e.g., cyclodextrine) or other generally recognized as safe (“GRAS”) excipients.

Examples of diseases, conditions or disorders that may be treated with 15 embodiments of the invention include, but are not limited to, asthma, COPD (chronic obstructive pulmonary disease), viral or bacterial infections, influenza, allergies, and other respiratory ailments as well as diabetes and other insulin resistance disorders. The dry powder inhalation may be used to deliver locally acting agents such as antimicrobials, protease inhibitors, and nucleic acids/oligonucleotides as well as systemic agents such as peptides like leuprolide and proteins such as insulin. For example, inhaler-based delivery of antimicrobial agents such as antitubercular 20 compounds, proteins such as insulin for diabetes therapy or other insulin-resistance related disorders, peptides such as leuprolide acetate for treatment of prostate cancer and/or endometriosis and nucleic acids or oligonucleotides for cystic fibrosis gene therapy may be performed. *See e.g.* Wolff et al., *Generation of Aerosolized Drugs*, J. Aerosol. Med. pp. 89-106 (1994). *See also* U.S. Patent Application Publication No. 25 20010053761, entitled *Method for Administering ASPB28-Human Insulin* and U.S. Patent Application Publication No. 20010007853, entitled *Method for Administering Monomeric Insulin Analogs*, the contents of which are hereby incorporated by reference as if recited in full herein.

Typical dose amounts of the unitized dry powder mixture dispersed in the 30 inhaler will vary depending on the patient size, the systemic target, and the particular drug. Conventional exemplary dry powder dose amount for an average adult is about 10-30 mg and for an average adolescent pediatric subject is from about 5-10 mg. A

typical dose concentration may be between about 1-2%. Exemplary dry powder drugs include, but are not limited to, albuterol, fluticasone, beclamethasone, cromolyn, terbutaline, fenoterol, β -agonists (including long-acting β -agonists), salmeterol, formoterol, cortico-steroids and glucocorticoids. In certain embodiments, the
5 administered bolus or dose can be formulated with an increase in concentration (an increased percentage of active constituents) over conventional blends. Further, the dry powder formulations may be configured as a smaller administerable dose compared to the conventional 10-25 mg doses. For example, each administerable dry powder dose may be on the order of less than about 60-70% of that of conventional
10 doses. In certain particular embodiments, using the active dispersal systems provided by certain embodiments of the DPI configurations of the instant invention, the adult dose may be reduced to under about 15 mg, such as between about 10 μ g-10mg, and more typically between about 50 μ g-10mg. The active constituent(s) concentration may be between about 5-10%. In other embodiments, active constituent
15 concentrations can be in the range of between about 10-20%, 20-25%, or even larger. In particular embodiments, such as for nasal inhalation, target dose amounts may be between about 12-100 μ g.

In certain particular embodiments, during dose dispensing, the dry powder in a particular dose receptacle may be formulated in high concentrations of an active
20 pharmaceutical constituent(s) substantially without additives (such as excipients). As used herein, “substantially without additives” means that the dry powder is in a substantially pure active formulation with only minimal amounts of other non-biopharmacological active ingredients. The term “minimal amounts” means that the non-active ingredients may be present, but are present in greatly reduced amounts,
25 relative to the active ingredient(s), such that they comprise less than about 10%, and preferably less than about 5%, of the dispensed dry powder formulation, and, in certain embodiments, the non-active ingredients are present in only trace amounts.

In certain embodiments, certain active elements are integral to/included as part of a disposable (replaceable) blister package. In other embodiments, the inhaler with
30 the drug blister package can itself be disposable after dispensing the doses provided by a blister package and/or may be configured with an integral active piezoelectric polymer member. In yet other embodiments, combinations of the above

configurations may be used. Unlike many conventional active dispersion systems, cleansing of the active mechanism portion of the inhaler may not be required. Examples of suitable inhalers are described in co-pending U.S. Patent Application Serial No. 10/434,009 and U.S. Patent Application Serial No. XXX, filed October 21, 5 2004, corresponding to U.S. Provisional Application No. 60/514,671, filed October 27, 2003, the contents of these documents are hereby incorporated by reference as if recited in full herein.

Figures 1A and 2 illustrate one exemplary blister package **15**. As shown in **Figure 2**, the blister package **15** includes a plurality of spaced apart blisters **15b**. The 10 blister package **15** can include a ceiling **16** with projections **16p** (*i.e.*, wells) overlying each blister **15b**, a frame member **17** (which in certain embodiments can be described as an intermediate member or "spacer") and a floor **18**. The frame member **17** can have a thickness that is greater than the combined thickness of the ceiling and floor **16, 18**, respectively. Typically, the frame member **17** will have a thickness that is at 15 least five times, and typically at least about ten times, and more typically at least about 15 times, greater than the thickness of either the floor **18** and/or ceiling **16**. Although shown with projections **16p** formed therein, in particular embodiments, the ceiling **16** may also be substantially planar over the apertures of the frame member **17** (and/or over the entire surface of the spacer member **17**). As shown, the frame 20 member **17** includes a plurality of spaced apart gap spaces or apertures **17a** extending therethrough, each having a depth that defines at least a portion of a sidewall **17w** (**Figure 3**) of a blister **15b**.

In certain embodiments, the ceiling **16** is configured to be removed, when in 25 position in an inhaler, to dispense the dry powder **100** held therein (**Figures 4A and 4B**). The ceiling **16** can comprise a relatively thin flexible material. In certain embodiments, the ceiling **16** comprises a flexible material layer that has sufficient structural rigidity so as to be able to have projections **16p** formed therein that retain their shape as shown in **Figure 1A** when in position. In addition, the ceiling is typically configured to inhibit moisture penetration to keep the dry powder, dry, for 30 the desired shelf and/or useful life of the dry powder (drug). For example, the ceiling **16** can contain foil (such as aluminum or other suitable material) and/or may be a laminated structure, comprising a polymer layer and a foil layer. In particular

embodiments, the ceiling **16** can comprise layers of polyamide film, aluminum foil, and polypropylene film (where the top layer may be the polyamide film) adhered to each other with a laminating adhesive. In certain embodiments, the ceiling **16** can have a thickness of between about 0.100-0.150 mm, and typically about 0.127 mm.

5 The projections **16p**, where used, may have a height that is between about 1- 5 mm and typically at least about 1.5 mm.

In other embodiments, such as shown for example in **Figure 1C**, the ceiling **16'** may be defined by an upper primary closed surface of the frame member **17'**. Alternatively, as shown in **Figure 1D**, a continuous or discrete planar sealant covering 10 can be placed over the apertures **17a** to define the ceiling **16'**. In the embodiments shown in **Figures 1C** and **1D**, the floor **18** can be formed of a flexible thin sealant layer that is configured for removal to release the dry powder. In some embodiments, the floor **18** and/or the ceiling **16'** can comprise a flexible piezoelectric polymer. In some embodiments, as shown for example in **Figure 1C**, a flexible piezoelectric 15 polymer material **60** can be configured in an inhalation flow path **40** but the ceiling **16'** and/or floor **18** may be devoid of a piezoelectric polymer material. In some embodiments, the ceiling **16'** can comprise a piezoelectric polymer as well as a portion of the flow path **40** to vibrate the dry powder during inhalation. In the embodiments shown in **Figures 1C** and **1D**, the floor **18** can include tabs **30** which 20 may be configured as loops **30a** to allow the dry powder in one or more apertures **17A** to be selectively released.

Referring again to **Figure 1A**, typically, the frame member **17** defines substantially the entire (typically all of the) sidewall **17w** of a respective blister **15b** (see, e.g., **Figures 4A** and **4B**) and extends a distance above the floor **18** and/or below 25 the ceiling **16**. The gap space or aperture **17a** can include a single sidewall **17w** when the geometric shape of the aperture is circular, oval, curvilinear (such as elongate channel) or other continuous shape. Alternatively, in other geometric configurations, the aperture **17a** can be configured with a plurality of contiguous sidewalls **17w** (i.e., a square, rectangle, triangle, wedge, or other multi-sided shape). **Figure 1A** 30 illustrates the aperture **17a** having an elongate curvilinear configuration (when viewed from the top and/or bottom). **Figures 5A-5C** illustrate a blister package **15** with a

ceiling **16** having semi-spherical projections **16p** and the frame member **17** having a substantially circular aperture **17a** (when viewed from the top and/or bottom).

As shown in **Figures 4A, 4B, and 5C**, the sidewall **17w** of the blister **15b** can angle or taper inward from top to bottom, with the surface area of the bottom of the aperture **17a** being less than that of the top of the frame member aperture **17a**. In particular embodiments, the sidewall **17w** can have an angle of inclination (that may be substantially constant) that is between about 15-60 degrees, and typically between about 20-40 degrees. The sealed blister **15b** is illustrated as enclosing a quantity of dry powder **100** therein.

In the embodiment shown in **Figure 1A**, the frame apertures **17a** have a perimeter shape **17p**. The perimeter shape **17p** is sized and configured to substantially correspond with the perimeter shape **15p** of the blister **15b** that is defined by that of the projecting ceiling **16p**. Thus, the aperture **17a** may have a shape and size that is substantially the same as the shape and size of a respective projecting overlying ceiling **16p** (where used).

The frame member **17** can have increased rigidity with respect to that of the floor **18** and/or ceiling **16**. In particular embodiments, the frame member **17** can be a substantially rigid light-weight member that provides structural integrity to the ceiling and floor **16, 18**. The ceiling **16** can be attached to an upper primary surface **17u** of the intermediate member **17** and the floor **18** can be attached to a lower primary surface **17b** of the frame member **17**. The frame member **17** may have a unitary body as shown or a laminated or stacked structure (not shown). In certain embodiments, the frame member **17** can be a molded polymer and/or fiber reinforced resin material. In particular embodiments, the frame member **17** comprises a natural homopolymer polypropylene and can typically be between about 1-3 mm thick, and is more typically about 2 mm thick. Other suitable materials or fabrication methods and thicknesses can also be used. The frame member **17** may include additional apertures, slots or depressions and the like to further decrease weight as suitable. The frame member **17** may be configured with sufficient thickness, material and/or coatings to provide a moisture barrier (inhibit moisture penetration) to the dry powder held in the blister as discussed above for the ceiling.

The ceiling and/or floor 16, 16', 18, respectively, can comprise a generally continuous sheet(s) or layer(s) of material as shown in **Figures 1A, 1B, 1D and 5A**. Alternatively, the ceiling and/or floor 16, 16', 18, respectively, may comprise non-continuous discrete segments of material forming a respective blister ceiling 16 and floor 18 that can be attached over and under each aperture 17a to define respective sealed blisters 15b (not shown).

Figures 1A and 1B illustrate that the floor 18 can include a plurality of abutting flexible and/or resilient layers 18i, shown as two different layers, a non-active layer 18₁ and an active layer 18₂. In particular embodiments, the active layer 18₂ may 10 be positioned above the non-active layer 18₁. The term "active" layer means that the layer comprises an electrically active material. In certain embodiments, the active layer 18₂ comprises a thin-film layer of a piezoelectric material, typically a polymer such as PVDF as will be described further below. In certain embodiments, additional floor layers may also be used (not shown). Alternatively, the floor 18 can be a single 15 layer configuration defined by the active layer 18₂ (also not shown). Similar to the ceiling 16, the floor 18 can be configured to inhibit moisture penetration (i.e., be configured to provide a moisture barrier at operating/exposure pressures for a desired length of time) into the blister space thereby keeping the dry powder dry and ready for flowable dispersion via inhalation. In addition, the portions of the floor 18 (i.e., such 20 as the upper surface) that contacts the dry powder should be configured to be compatible therewith (i.e., chemically and/or physically).

It is noted for clarity that features described for one embodiment may be used in conjunction with another embodiment although not specifically discussed with respect to a different embodiment. For example, the frame structure and/or the floor 25 and/or ceiling of the embodiments shown in **Figures 1C and 1D** may comprise a laminated or active structure discussed with respect to the embodiments shown in one or more of **Figures 1A, 5, 8, 11 and 12**.

Typically, when a plurality of floor layers 18i are used, the floor layers 18i (such as, for example 18₁, 18₂) are attached to each other so that flexure (up and 30 down) of one layer causes the other(s) to substantially concurrently flex up and down in response thereto. The floor layers 18i can be configured so that the flexing of the active layer 18₂ is not substantially reduced or insulated by the other contacting layer

(s) to thereby provide a desired vibratory dispersion input to the dry powder **100** in a blister **15b** during active inspiration. The floor layers **18₁**, **18₂** can be a laminated structure or otherwise attached over a sufficient surface area to facilitate substantially concurrent flexing at a floor **18** of a respective blister **15b** to thereby vibrate dry powder held therein during operation. The non-active portion or layers of the floor **18** may include material(s) similar to that described for the ceiling **16** above. The floor layers **18₁**, **18₂** may be adhesively attached, heat and/or pressure bonded, or otherwise attached.

The non-active layer **18₁** can include foil, typically aluminum foil, and may, in certain embodiments, include a polymer coating or layer on the top and/or bottom thereof. Typically the non-active portion of the floor **18₁** will be at least about 20 microns thick. Coatings and/or other materials can be used to inhibit moisture penetration (*i.e.*, act as a moisture barrier) into the sealed blister cavity and/or to aid in sealing (*i.e.*, adhering) the floor **18** to adjacent structures or layers. One suitable material is available from Hueck Foils, located in Blythewood, South Carolina.

In particular embodiments, the non-active layer **18₁** may be attached using a relatively thin foil-release material such as a release film. The release film can be used to transfer a pressure sensitive adhesive (PSA) to a desired layer (such as shown in **Figure 19C**) that can be used to attach two layers together. The upper surface **18u** of the non-active layer **18₂** may define the dry powder contact surface of the blister **15b** as shown in **Figure 3** and can be attached to the active layer **18₂** that can comprise the piezoelectrically active material.

As shown in **Figures 1A** and **1B**, the active layer **18₂** can be configured with a predetermined conductive pattern **18p**. The pattern **18p** can include a plurality of spaced apart segments **18s** sized, configured and aligned to be positioned under a bottom of each blister **15b**. The pattern **18p** can also include at least one electrical (signal) trace **18t** leading from the segment **18s** to an electrical contact zone **18z**. The electrical contact zone **18z** is shown as centrally positioned on the active layer **18₂**; however, other electrical contact zone configurations and locations can be used. In those embodiments, alternative access through, on or around the frame member **17** may be provided. As such, the frame member **17** may be molded or formed into other shapes without a center aperture and/or different access configurations.

For example, **Figures 8D** and **8E** illustrate conductive patterns **18p'** with contact zones **18z** located proximate an outer perimeter of the blister package. **Figure 8D** illustrates that each blister may have its own contact zone for individual selective activation (individually addressable blisters) or excitation of a target blister in operation. **Figure 8E** illustrates a different blister shape and also that respective pairs of blisters may share a common contact zone **18z** with traces **18t** for each blister traveling toward each other and merging to the common contact zone **18t**. Other numbers of blisters can be electrically grouped and/or the contact zones may be positioned at other locations. The plurality of shared contact zones **18z**, one for each pair of blisters, may be particularly suitable for use in combinatorial dispersion configurations, such as those shown in **Figures 7A-7C**.

In some embodiments, in operation, a predetermined electrical signal can be applied to the active layer **18z** to flex the floor of the blister **15b** and vibrate the powder **100** held therein (**Figures 4A, 4B**). The electrical signal is transmitted to the blister **15b** in a dispensing location via the conductive pattern **18p** (such as via the conductive zone **18z** to the trace **18t** and the segment **18s** under the blister **15b**). In the embodiment shown in **Figures 1A** and **1B**, a plurality of blisters **15b** may be in electrical communication with a signal generator **200** (**Figure 13**) and concurrently flexed. In other embodiments, the predetermined pattern **18p** can be configured so that a selective blister **15b** can be flexed (not shown). In the latter, the contact zone **18z** may be configured as a discrete contact zone for each blister **15b**. A regional contact zone **18z** may also be provided to electrically communicate with a plurality of blisters (not shown). Electrical insulation or discontinuous conductive patterns **18p** can be used to provide electrical separation as is well known to one of skill in the art. The contact zone **18z** may be otherwise located, such as at an outer or inner edge of the pattern **18p** to communicate with the signal generator **200**. The signal generator **200** (such as that shown in **Figure 13**) may be integrated with the blister package **15b** or held in the inhaler so as to engage the active floor layer **18z** in operation.

The predetermined pattern **18p** can comprise a conductive material such as metal. The conductive material can be a thin layer of metal or other conductive material that can be inked, stamped, printed (including screen printed), imaged (including, but not limited to, photo-resist imaging), rolled, deposited, sprayed, or

otherwise applied to (one or both primary surfaces of) the active layer **18₂**. Other methods of providing the conductive pattern **18p** can also be used, including electron beam evaporation, thermal evaporation, painting, dipping, or sputtering a conductive material or metallic paint and the like or material over the selected surfaces of the piezoelectric substrate (preferably a PVDF layer as noted above). In particular embodiments, alternative metallic circuits, foils, surfaces, or techniques can also be employed, such as attaching a conductive mylar layer or flex circuit over the desired portion of the outer surface of the piezoelectric substrate layer. If flex circuits are used, they may be configured or attached to the piezoelectric substrate layer so as to be substantially transparent to the structure to reduce any potential dampening interference with the substrate layer.

Typically, upper and lower surface metal trace patterns are formed on opposing sides of a piezoelectric polymer material layer but do not connect or contact each other. For example, conductive paint or ink (such as silver or gold) can be applied onto the major surfaces of the package about the elongated channels and associated metal traces such that it does not extend over the perimeter edge portions of the piezoelectric substrate layer, thereby keeping the metal trace patterns on the top and bottom surfaces separated with the piezoelectric substrate layer therebetween. This configuration forms the electrical excitation path when connected to a control system to provide the input/excitation signal for creating the electrical field that activates the deformation of the piezoelectric substrate layer during operation. Typically, one pattern **18p** is applied to one side of the active floor **18₂** and the other side may have a different conductive pattern and/or coverage.

Figure 1A illustrates that the active layer **18₂** may have a different configuration than the first floor layer **18₁**. **Figures 1B** and **8A** illustrate that the first floor layer **18₁**, the frame member **17** and the ceiling **16** may be configured with substantially the same shape and size (shown as substantially circular) when viewed from the top, and have aligned center spaces or apertures **16c**, **17c**, **18_{1c}**, that when assembled provide an access window **15w** that exposes a center portion **18_{2c}** (**Figure 2, 3, 5B**) of the top surface of the second or active floor layer **18₂**. Where edge contact zones or other electrical contact configurations are used, the center window **15w** to the active layer **18₂** may not be used.

5 **Figure 5C** illustrates that the active floor layer **18₂** can be substantially coextensive at least about an outer perimeter portion of the blister package **15** while **Figures 4A** and **4B** illustrate that the active floor layer **18₂** can be discontinuous at the outer perimeter portion of the blister package **15**. **Figures 4B** and **5C** also illustrate that the floor **18** of a respective blister **15b** can be substantially planar about the frame member gap space or aperture **17a** while **Figure 4A** illustrates that the floor **18** may be configured with a recession **18r** therein (formed by at least the first layer **18₁** and in some instances a depression in the piezoactive layer **18₂** conformally thereunder (not shown)).

10 **Figure 1A** illustrates that the active layer **18₂** may cover or have less surface area than the first floor layer **18₁** of the blister package **15**. **Figure 1B** illustrates that the first and second floor layers **18₁, 18₂** can be substantially coextensive with each other (at least over a major portion of the configurations thereof away from the center portions) with the first layer **18₁** having an aperture **18_{1c}** that exposes or provides 15 electrical contact with the underlying active layer **18₂**. It is noted that **Figure 1B** is shown without a full conductive pattern **18p**. As shown in **Figures 5A** and **8A**, the active layer **18₂** can be a continuous layer of film that is substantially circular. Other configurations may be used.

20 In the embodiment shown in **Figures 8A-8C**, one of the primary surfaces of the active layer **18₂** may have a first predetermined conductive pattern **18p₁** as shown in **Figures 8C** and **8D** while the other surface can have a different second predetermined conductive pattern **18p₂** as shown in **Figure 8A**. The second conductive pattern **18p₂** shown in **Figure 8A** illustrates that substantially the entire primary surface can be conductive (*i.e.*, metallized). In particular embodiments, the 25 first predetermined pattern **18p₁** may be oriented to be the upper surface configured to contact the underside of the first floor layer **18₁** (or the frame member **17**, where the active layer defines the floor of a blister) with the second pattern **18p₂** oriented away from the first floor layer **18₁**. The reverse orientation may be used in other embodiments. Further, as noted above, in yet other embodiments, the second layer 30 **18₂** may be used without the first layer **18₁** so as to define the floor of the blister **15b**.

 In certain embodiments, the active layer **18₂** includes a piezoelectric polymer material that can be formed from a piezoelectrically active material such as PVDF

(known as KYNAR piezo film or polyvinylidene fluoride) and its copolymers or polyvinylidene difluoride and its copolymers (such as PVDF with its copolymer trifluoroethylene (PVDF-TrFe)).

In particular embodiments, the piezoelectric polymer material comprises a 5 layer of a thin PVDF film. As used herein, the term “thin film” means that the piezoelectric polymer layer is configured as a structurally flexible or pliable layer that can be sized to be about 10-200 μm thick. In certain embodiments, the piezoelectric polymer layer can be sized to be less than about 100 μm thick, typically about 20-60 μm thick, and more typically about 28 μm .

10 As noted above, selected regions of the piezoelectric polymer material can be coated or layered with a conductive material to form a desired conductive pattern 18p. The conductive regions (at least portions of the blister regions) of the floor 18 define the active regions and can be individually or selectively activated during operation. Although shown as forming the bottom layer of the floor 18₂, the PVDF may form the 15 bottom, top, or an intermediate layer of the laminated material structure. For intermediate layer configurations, vias and/or edge connections can be used to apply the electric signal to the blister piezoelectric material.

20 The excitation circuit (signal generating circuitry) configuration can be such that the one surface operates with a positive polarity while the other surface has a negative polarity or ground, or vice versa (thereby providing the electric field/ voltage differential to excite the piezoelectric substrate in the region of the selected blister 15b). Of course, the polarities can also be rapidly reversed during application of the excitation signal (such as + to -, or + to -) depending on the type of excitation signal used, thereby flexing the piezoelectric material in the region of the receptacle portion. 25 For a more complete discussion of the active excitation path or configuration, *see* U.S. Application Serial No. 10/204,609, incorporated by reference herein.

Figure 6 illustrates that a mounting member 50 may be attached to the blister package 15. The mounting member 50 can be configured to engage an inhaler to hold the blister package 15 in position therein while allowing the blister package 15 to 30 rotate to present a blister 15b for dispensing via the inhaler. The mounting member 50 may be integrally mounted or formed onto the blister package 15 (by, for example, bonding or molding to the body of the frame member 17). The mounting member 50

may be sized and configured to reside over (within and/or above) the blister window 15w. The mounting member 50 may use tabs 52 or other mechanisms to attach to the blister package 15 so that the blister package 15 rotates with the mounting member 50 when in position in the inhaler. **Figure 6** also illustrates that certain operational 5 components can be held by the mounting member 50. For example, a battery 210 (such as a pancake-like and/or small digital camera type battery) and a signal generator 200 or components thereof. The mounting member 50 can include electrical leads or traces that extend from the signal generator 200 to the active floor layer 18₂. The gear 50g can include a bore 50b therein which can be configured to 10 allow access to an exposed surface of the active layer 18₂.

In particular embodiments, the mounting member 50 can be configured as a rotatable gear 50g with gear teeth 50t (**Figure 9**) that mounts in the inhaler. In operation, a pawl or other indexing mechanism contacts one or more gear teeth 50t to 15 so as to controllably rotate the gear 50g and thereby advance the blister package 15 therewith to position a blister 15b at a blister dispensing location in the inhaler. *See* co-pending U.S. Patent Application Serial No.XXX identified by Attorney Docket No. 9336-13, filed October 21, 2004, the contents of which were hereby incorporated by reference above as if recited in full herein.

Figures 7A-7C illustrate alternative configurations of the frame member 17 20 with closely spaced neighboring intermediate member apertures 17a₁, 17a₂ that define a sidewall(s) of corresponding blisters 15b₁, 15b₂ (not shown) which can be used to concurrently dispense the dry powder in neighboring blisters for combination therapeutic treatments. The neighboring apertures 17a₁, 17a₂ (which may be pairs or 25 sets of three or more apertures) may be spaced closer together on the intermediate member 17 than the non-neighboring apertures. **Figures 1C and 1D** illustrate generally concentrically aligned pairs of apertures 17a₁, 17a₂. Each adjacent or neighboring blister 15b₁, 15b₂ may contain different medicaments and/or dry powders therein that can be concurrently released upon inhalation during operative use.

Figure 7A illustrates side by side, neighboring (adjacent) pairs of apertures 17a₁, 17a₂ 30 that form the sidewall(s) of corresponding blisters 15b₁, 15b₂ (not shown) that are configured to be jointly dispersed upon inhalation in an inhaler. **Figure 7B** illustrates front to back neighboring blister sidewalls 17a₁, 17a₂ that can also be configured to be

jointly dispersed upon inhalation via an inhaler. **Figure 7C** illustrates yet another side-by-side configuration with neighboring elongate apertures **17a₁**, **17a₂**. In certain embodiments, the side-by-side aperture/blister configurations may be offset lengthwise (not shown) across the blister package.

5 **Figures 9-12B** illustrate an alternative embodiment of a blister package **15'**. As shown, the blister package **15'** includes the ceiling **16** that has a body that resides below a frame **117**. The frame **117** overlies the ceiling **16** and includes a plurality of apertures **117a** that are sized and configured to allow the blister ceiling projections **16p** to extend therethrough. The frame **117** can be configured to resist flexure and/or 10 have increased rigidity relative to the floor **18** and/or ceiling **16** of the blister package. The frame **117** can have a thickness that is greater than the combined thickness of the ceiling **16** and floor **18**. The frame **117** can have a molded body comprising a polymer material. The frame **117** may be between about 0.25-2 mm thick, and typically between about 0.5-1 mm thick. In certain embodiments, the frame **117** may 15 be substantially rigid. The frame **117** can have a substantially planar top and bottom surface **117t**, **117b** (**Figure 11**).

In certain embodiments, the ceiling projections **16p** are configured to rise above the top surface **117t** of the frame **117** a desired distance. As shown in **Figures 12A** and **12B**, the ceiling projection **16p** may rise a distance "H" above the frame **117** 20 between about 1-10 mm, typically at least about 2 mm. As shown, the blister **15b** is formed by the sealing of the floor **18** with the ceiling **16** (the frame **117** does not form the sidewalls of the blister). The floor **18** of the blister **15** may be recessed as shown in **Figure 12B** or substantially planar such as shown in **Figure 12A**.

The ceiling **16** and floor **18** can be configured as described above. **Figure 11** 25 illustrates that the floor **18** may include a plurality of flexible layers, shown as two floor layers, **18₁**, **18₂**, as discussed above.

Figure 9 illustrates that the blister package **15'** may include a mounting member **50'** thereon. As discussed above, the mounting member **50'** can include a gear **50g** with gear teeth **50t** that engage an indexing mechanism in the inhaler as 30 discussed above. As before, the mounting member **50'** may be integrally attached to, formed on, or releasably attached to the frame **117** to form a blister package **15'**. In other embodiments, as shown in **Figure 10** the blister package **15'** is not required to

include a mounting member. The gear **50g** can include a bore **50b** therein which can be configured to allow access to an exposed surface of the active layer **182**. The inhaler may include a pin that engages the bore of the gear to hold the gear and blister package in position and allow the gear **50g** to rotate in the inhaler. The blister frame 5 **117** and blister package **15'** may be configured as a replaceable modular unit for an inhaler. In particular embodiments, the blister frame **117**, the gear **50g** and the blister package **15'** are a modular unit that is disposable after the blisters have been depleted and the inhaler is configured to allow replacement thereof.

It is noted that other and/or additional mounting structures beyond those 10 shown in the figures may be used to configure the blister package **15** for use in an inhaler. It is also noted that the shape of the blisters **15b** is not limited to that shown in the embodiments described herein. In particular embodiments, the blister package **15, 15'** may be configured to have a substantially disk-like shape. The blister package **15, 15'** can be configured to rotate in the inhaler to advance a respective blister into an 15 indexed or registered inhalation position.

In the embodiment shown in **Figure 11**, the frame **117** can include a plurality of frame apertures **117a**, each with a perimeter shape **117p**. The perimeter shape **117p** is sized and configured to allow the projecting ceiling **16p** of the blister **15b** to extend therethrough. The frame aperture perimeter shape **117p** may be configured to 20 substantially correspond to the blister perimeter shape **15p** when viewed from the top. Thus, the frame aperture **117a** may have a shape and size that is substantially the same as the shape and size of a respective blister **15b**. The blister **15b** can have a width and length and the aperture **117a** can have substantially the same width and length (typically just a bit larger than the width/length of the blister).

25 In certain embodiments, the blister package **15, 15'** can include visible indicia and/or can be configured to engage an inhaler to provide audible alerts to warn a user that he/she is approaching the last of the filled blister inhalant doses on the blister package **15, 15'** and/or to indicate that the dose was properly (and/or improperly) inhaled or released from the inhaler device. For example, certain dry powder dose 30 sizes are formulated so that it can be difficult for a user to know whether they have inhaled the medicament (typically the dose is aerosolized and enters the body with little or no taste and/or tactile feel for confirmation). Thus, a sensor can be positioned

in communication with a blister **15b** in a dispensing position in an inhaler and configured to be in communication with a digital signal processor or microcontroller, each held in or on the inhaler and/or the blister package **15, 15'**. In operation, the sensor is configured to detect a selected parameter, such as a difference in weight, a density in the exiting aerosol formulation, and the like, to confirm that the dose was released.

In certain embodiments, the blister package **15, 15'** can include color-enhanced markings for the last few (such as the last 5) doses. The color-enhanced markings may change from darker (orange to salmon or red) or to completely different colors as the last dose or last few doses approach. Alternatively (or additionally), the multi-dose disposable package **15, 15'** may be configured with audible alert features that activate a digital signal processor or micro-controller (not shown) housed in the inhaler to generate a stored audible verbal message or warning (such as "warning, refill needed, only five doses remain") when a desired number of doses have been administered.

In certain embodiments, in position, a forward or leading (cutting) edge portion of a blade can be configured to open (typically cut or slice) at least a portion of the projecting ceiling **16p** of a blister **15b, 15b'** by traveling generally (typically substantially) parallel to a plane extending horizontally about an upper portion of an underlying blister along a length direction thereof at a position that is less than the height of the blister projection, to slice a major portion of the ceiling in the length direction, forming a gap space to allow the dry powder held in the blister **15b, 15b'** to be dispensed.

Figure 13 illustrates an example of a signal generator **200** that may be configured to reside in and/or communicate with the blister package **15, 15'**. The signal generator can include a processor (such as a digital signal processor) **215** and electronic memory **222**. The electronic memory can include, but is not limited to, cache, ROM, PROM, EPROM, EEPROM, flash memory, SRAM, and DRAM.

The signal generator **200** may, in certain embodiments, also include a powder specific non-linear signal generator computer program module **220** that provides the electrical signal characteristics for the drug being dispensed. The module **220** may be programmed into the memory **222**. The signal generator **200** may have a sleep or

inactive (or off) mode that is turned to an active mode based on inhaler activation via input from a switch or a sensor 223. For example, the signal generator 200 may communicate with a power source 10 such as a battery (typically a miniaturized battery, such as a digital camera or pancake type flat battery) to power the signal generator and transmit the electrical signal to the desired blister 15b, 15b'. The activation may be carried out automatically based upon input from a sensor and/or activation from an "on" switch.

5 Examples of an amplitude-modified vibratory signal suitable for vibrating the blister 15b, 15b' holding the dry powder are described in co-pending U.S. Patent 10 Application Serial No. 10/434,009, the contents of which are incorporated by reference as if recited in full herein. The vibratory signal can include a kHz carrier frequency (such as about 5kHz-50kHz) modified by low modulating frequency (typically about 10-200Hz). The frequency of the vibration can be modified to match or correspond to the flow characteristics of the dry powder substance held in the 15 package to attempt to reach a resonant frequency(s) to promote uniform drug dispersion into the body. In some embodiments, a non-linear powder-specific dry powder vibratory energy signal a different powder specific signal for each of the formulations on a blister package or the same for a particular formulation on each package) comprising a plurality of selected frequencies can be generated 20 (corresponding to the particular dry powder being currently dispensed) to output the particular signal corresponding to the dry powder then being dispensed. As used herein, the term "non-linear" means that the vibratory action or signal applied to the package to deliver a dose of dry powder to a user has an irregular shape or cycle, typically employing multiple superimposed frequencies, and/or a vibratory frequency 25 line shape that has varying amplitudes (peaks) and peak widths over typical standard intervals (per second, minute, etc.) over time. In contrast to conventional systems, the non-linear vibratory signal input can operate without a fixed single or steady state repeating amplitude at a fixed frequency or cycle. This non-linear vibratory input can be applied to the blister to generate a variable amplitude motion (in either a one, two 30 and/or three-dimensional vibratory motion). The non-linear signal fluidizes the powder in such a way that a powder "flow resonance" is generated allowing active flowable dispensing.

The blister package 15, 15' can include signal-generating circuitry and/or components held thereon or therein which, in operation, are in communication with the blisters 15b, 15b' (via the conductive pattern 18p on the active floor 18₂). The signal generating circuitry may be programmed with a plurality of predetermined 5 different input signals, or if the blister package dispenses only a single dry powder, the signal generator may be programmed with a single signal. Appropriate powder-specific signals can be determined experimentally and/or computationally at an OEM or evaluation site and input into the inhalers (via hardware and/or software components including programmable processors). For additional description of 10 signals and operations to determine same, see co-pending and co-assigned U.S. Patent Application Serial Nos. 10/434,009, 10/606,678, 10/607,389, and 10/606,676: the contents of these applications are hereby incorporated by reference in their entireties 15 as if recited in full herein.

In some embodiments, a signal of combined frequencies can be generated to 15 provide a non-linear signal to improve fluidic flow performance. Selected frequencies can be superimposed to generate a single superposition signal (that may also include weighted amplitudes for certain of the selected frequencies or adjustments of relative amplitudes according to the observed frequency distribution). Thus, the vibratory signal can be a derived non-linear oscillatory or vibratory energy signal used to 20 dispense a particular dry powder. In certain embodiments, the output signal used to activate the piezoelectric blister channel may be include a plurality (typically at least three) superpositioned modulating frequencies and a selected carrier frequency. The modulating frequencies can be in the range noted herein (typically between about 10-500 Hz), and, in certain embodiments may include at least three, and typically about 25 four, superpositioned modulating frequencies in the range of between about 10-100Hz, and more typically, four superpositioned modulating frequencies in the range of between about 10-15Hz.

Generally describing some embodiments, in operation, the blister packages 15, 15' are configured to operate with dry powder inhalers. The inhalers can be used for 30 nasal and/or oral (mouth) respiratory delivery. The inhalable dry powder doses can be packaged in multi-dose dry powder drug packages that may include a piezoelectric polymer substrate (such as PVDF) that flexes to deform rapidly and provide

mechanical oscillation in an individually selectable signal path on the package. The signal path directs the signal to the region of the drug receptacle or well to cause the well to oscillate in cooperation with a user's inspiratory effort, and, thus, actively direct the dry powder out of the well and up into the exit flow path.

5 **Figure 14** is a block diagram of exemplary embodiments of data processing systems that illustrate an example of a computer program product module 220 of **Figure 13** in accordance with embodiments of the present invention. The module 220 may be configured to provide powder specific or other types of electrical signal input signals. The processor 410 communicates with the memory 414 via an address/data 10 bus 448. The processor 410 can be any commercially available or custom microprocessor. The memory 414 is representative of the overall hierarchy of memory devices containing the software and data used to implement the functionality of the data processing system 405. The memory 414 can include, but is not limited to, the following types of devices: cache, ROM, PROM, EPROM, EEPROM, flash 15 memory, SRAM, and DRAM.

As shown in **Figure 14**, the memory 414 may include several categories of software and data used in the data processing system 405: the operating system 452; the application programs 454; the input/output (I/O) device drivers 458; a powder (specific) signal generator (vibratory) module 220; and the data 456. The data 456 20 may include: (a) a look-up chart/table data for dry powder signal formulations for plurality of different dry powders 451; (b) *in situ* acquired measurement data whether to confirm that the dry powder dose was properly (or improperly) dispensed and/or patient inspiratory data, which may be obtained from an operator or stored by the inhaler; (c) and/or timing data that automatically activates the signal and inputs to the 25 blister for dispensing the dry powder based upon a pull operation (pulling the cutting cartridge and/or mouthpiece outward). As will be appreciated by those of skill in the art, the operating system 452 of the inhaler, blister package 15, 15' and/or programmable inputs thereto may be any operating system suitable for use with a data processing system, such as OS/2, AIX, OS/390 or System390 from International 30 Business Machines Corporation, Armonk, NY, Windows CE, Windows NT, Windows95, Windows98 or Windows2000 from Microsoft Corporation, Redmond, WA, Unix or Linux or FreeBSD, Palm OS from Palm, Inc., Mac OS from Apple

Computer, LabView, or proprietary operating systems. The I/O device drivers 458 typically include software routines accessed through the operating system 452 by the application programs 454 to communicate with devices such as I/O data port(s), data storage 456 and certain memory 414 components and/or the dispensing system 420.

5 The application programs 454 are illustrative of the programs that implement the various features of the data processing system 405 and preferably include at least one application which supports operations according to embodiments of the present invention. Finally, the data 456 represents the static and dynamic data used by the application programs 454, the operating system 452, the I/O device drivers 458, and 10 other software programs that may reside in the memory 414.

While the present invention is illustrated, for example, with reference to the powder signal generator module 220 being an application program in **Figure 14**, as will be appreciated by those of skill in the art, other configurations may also be utilized while still benefiting from the teachings of the present invention. For 15 example, the module 220 may also be incorporated into the operating system 452, the I/O device drivers 458 or other such logical division of the data processing system 405. Thus, the present invention should not be construed as limited to the configuration of **Figure 14**, which is intended to encompass any configuration capable of carrying out the operations described herein.

20 The I/O data port can be used to transfer information between the data processing system 405 and the inhaler dispensing system 420 or another computer system or a network (e.g., the Internet) or to other devices controlled by the processor. These components may be conventional components such as those used in many conventional data processing systems which may be configured in accordance with 25 the present invention to operate as described herein.

While the present invention is illustrated, for example, with reference to particular divisions of programs, functions and memories, the present invention should not be construed as limited to such logical divisions. Thus, the present invention should not be construed as limited to the configuration of **Figure 14** but is 30 intended to encompass any configuration capable of carrying out the operations described herein.

Figure 15 illustrates an example of operations that can be carried out to fabricate a blister package 15 such as that shown in Figures 1A, 1B, 5A, 6, and 7A-7C according to embodiments of the present invention. Wells (*i.e.*, projections that are wells when the ceiling is inverted from the configuration shown certain of the figures such as in Figure 1A) can be formed in the ceiling material (**block 300**). As noted above, the ceiling material may be a relatively thin laminated structure. The wells can be filled with a predetermined amount of dry powder (**block 305**). The term "filled" includes providing an amount that is less than the volumetric capacity of the well. The ceiling material may be sterilized prior to (and/or after the wells are formed and/or prior to depositing the dry powder therein) (**block 351**). An intermediate member having a substantially rigid body with opposing upper and lower primary surfaces and a thickness with apertures extending therethrough can be aligned with the ceiling so that a respective aperture aligns with a respective well (**block 310**). The intermediate member upper primary surface can be sealed to the ceiling material (**block 315**) and the opposing primary surface sealed to the floor comprising a piezoelectric material to define sealed blisters with the dry powder captured therein (**block 320**).

The floor can be sealed to the intermediate member after the intermediate member is aligned with and/or sealed to the ceiling (**block 321**). Alternatively, the floor can be sealed to the intermediate member before the intermediate member is aligned with and/or sealed to the ceiling (**block 322**). In addition, the intermediate member can be attached to the ceiling before the dry powder is positioned therein or after the dry powder is held therein. If the latter, the intermediate member is attached to the ceiling while the projections are facing down with the wells holding the dry powder. If the former, the ceiling can be a planar sheet (not requiring projections or wells) as the intermediate member can define a well sized to hold dry powder therein. The sheet of ceiling material can be cut into a predetermined shape after the dry powder is placed in the wells (**block 307**). If so, a sheet of a first floor layer can be used to seal the intermediate member and the first floor layer sheet cut concurrently with the ceiling material into a desired shape. In other embodiments, the ceiling material and floor can be separately formed into desired shapes prior to attachment.

As described above, mounting and/or electrical components can be assembled to the blister package.

5 **Figure 16** illustrates operations that can be used to fabricate blister packages **15b'** (such as shown in **Figures 9-12**). As before, wells can be formed into the ceiling material (**block 350**). The wells can be filled with a desired amount of dry powder (**block 355**). A floor comprising a piezoelectric polymer material can be sealed to the ceiling to define sealed blisters with the dry powder captured therein (**block 360**). The ceiling (and floor) can be sterilized (**block 351**).

10 In certain embodiments, the floor can include first and second layers, the second layer comprising the piezoelectric polymer. The first layer can be a flexible material (*i.e.*, lid stock and/or foil release material) that can be sealed to the ceiling to seal the blisters with the dry powder held therebetween and then the second layer can be attached to the first floor layer (**block 361**).

15 As before, the sheet of ceiling material can be cut into a predetermined shape after the dry powder is placed in the wells (**block 357**). The first floor layer can be cut into substantially the same shape as the ceiling prior to and/or after attaching to the ceiling holding the dry powder (**block 363**). If the latter, a sheet of the first floor layer can be cut concurrently with the ceiling material into a desired shape. The ceiling and floor layer can have a disk-like shape with center apertures and the second 20 floor layer can have a substantially circular body with a greater surface area than that of the ceiling and or first layer of the floor (**block 362**). In other embodiments, the ceiling material and floor can be separately formed into desired shapes prior to attachment. As described above, mounting and/or electrical components can be assembled to the blister package.

25 **Figure 17A** illustrates operations that may be used to fabricate a primary blister package to which a piezoelectric material may be subsequently applied according to some embodiments of the present invention. As shown, blister wells can be formed in a ceiling material sheet (**block 370**). **Figure 17B** illustrates a ceiling sheet **16sh** with the sheet oriented with the projections **16p** down to define the wells **16w**. As shown in **Figure 17A**, the wells **16w** can be filled with dry powder (**block 372**). **Figure 17C** illustrates the dry powder **100** in the wells **16w**. The first floor layer of the floor, which can comprise a foil, is heat sealed to the ceiling and the

sealed structure cut into a desired shape (**block 374**) and **Figure 17D**. The blister package can undergo a content uniformity assessment or inspection (**block 376**). If the blister package passes, the blister package can proceed to piezoelectric lamination operation (**block 378**). If the blister package fails, the package is rejected, the cause 5 may be identified so that the process can be adjusted and/or corrective action taken as needed (**block 379**).

Figure 18 illustrates exemplary operations for providing a suitable piezoelectric or active floor layer. A sheet of PVDF can be obtained with a predetermined conductive pattern on a selected primary surface thereof (**block 380**). 10 The predetermined conductive pattern can be formed on the selected primary surface (**block 381**) or pre-configured thereon. The PVDF layer can be attached to a flexible first floor layer (**block 385**). As noted above, the PVDF layer can be applied to the first layer after the first layer is sealed to the ceiling (or intermediate member) or before.

15 In certain embodiments, the PVDF sheet can be metallized (coated, formed, or otherwise deposited with a thin metal layer) that can substantially cover both primary surfaces (typically not the minor surfaces) and the conductive pattern formed by selectively removing a portion of the metal on the selected primary surface (**block 383**). In other embodiments, the conductive pattern can be screen printed on the 20 PVDF sheet (**block 382**). However, as noted above other conductive pattern formation techniques may also be used.

The PVDF sheet can be formed into a desired shape (**block 384**). The shape can be formed prior to or after the formation of the conductive pattern. The shape of the PVDF floor layer can be substantially circular (and planar). The flexible floor 25 layers can be securely attached to define a flexible substantially laminated floor (**block 386**). The first floor layer can be attached after the first floor layer is sealed to the ceiling and/or intermediate member (**block 387**). The PVDF layer may be adhesively attached, heat and/or pressure bonded or otherwise attached. The conductive pattern may be oriented to face the first floor layer (**block 388**).

30 **Figure 19A** illustrates operations to form a multi-layer flexible floor with PVDF according to some particular embodiments of the present invention. As shown, a disk or other desired shape can be cut from PVDF material that has been metallized

(block 390). The metallization can be selectively removed from one primary surface (block 391). **Figure 19B** illustrates the two opposing primary surfaces of the active floor layer 18₂, one having metallization over substantially its entire surface and the other having the predetermined conductive pattern formed by the selective removal.

5 A plurality of the shaped floor pieces can be positioned on a common pressure sensitive adhesive (PSA) carrier or transfer liner 188 as shown in **Figure 19C**. PSA can be applied to one of the primary surfaces of the shaped floor layer 18₂ members and compressed to transfer PSA to the contact surface (block 392). The floor members 18₂ can be further cut or formed to a desired (primary) package size (block 10 393). **Figure 19D** illustrates the floor layers 18₂ with a backing liner of surface adhesive 18_{2s} thereon. The floor layers 18₂ can be (electrically) tested for signal integrity (such as circuit transmission paths and/or noise) (block 394). The testing can be carried out prior to applying the adhesive or without removing from the common carrier liner. If acceptable, the floor 18₂ can be separated from the liner, a 15 floor member 18₂ can be aligned with a blister package 15, 15' and pressure applied to attach the floor layer 18₂ thereto (block 395). If the floor layer 18₂ fails the test, the floor 18₂ is rejected (block 396) (and discarded or repaired). **Figure 19E** illustrates a finished package 15, 15' with the floor layer 18₂ attached to the bottom of the primary package with the sealed blisters.

20 Certain operations may be automated and/or carried out using computer programs and automated equipment.

The flowcharts and block diagrams of certain of the figures herein illustrate the architecture, functionality, and operation of possible implementations of dry powder-specific dispensing and/or vibratory energy excitation means according to the 25 present invention. In this regard, each block in the flow charts or block diagrams represents a module, segment, or portion of code, which comprises one or more executable instructions for implementing the specified logical function(s). It should also be noted that in some alternative implementations, the functions noted in the blocks may occur out of the order noted in the figures. For example, two blocks 30 shown in succession may in fact be executed substantially concurrently or the blocks may sometimes be executed in the reverse order, depending upon the functionality involved.

In certain embodiments, the powder specific vibration energy signals are non-linear and the inhaler can include computer program code that automatically selectively adjusts the output of the vibration energy signal based on the identified dry powder being dispensed. The vibration energy output signals for the dry powders 5 being dispensed can be based on data obtained from a fractal mass flow analysis or other suitable analysis of the dry powder being administered to the user. The inhaler may be particularly suited to dispense low-density dry powder.

The foregoing is illustrative of the present invention and is not to be construed as limiting thereof. Although a few exemplary embodiments of this invention have 10 been described, those skilled in the art will readily appreciate that many modifications are possible in the exemplary embodiments without materially departing from the novel teachings and advantages of this invention. Accordingly, all such modifications are intended to be included within the scope of this invention as defined in the claims. In the claims, means-plus-function clauses, where used, are intended to cover the 15 structures described herein as performing the recited function and not only structural equivalents but also equivalent structures. Therefore, it is to be understood that the foregoing is illustrative of the present invention and is not to be construed as limited to the specific embodiments disclosed, and that modifications to the disclosed embodiments, as well as other embodiments, are intended to be included within the 20 scope of the appended claims. The invention is defined by the following claims, with equivalents of the claims to be included therein.